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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,477	12/11/2001	Masahiro Imoto	1830/50521	4095

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EXAMINER

RAO, DEEPAK R

ART UNIT	PAPER NUMBER
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1624

10

DATE MAILED: 05/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

SM

Office Action SummaryApplication No.
10/009,477Applicant(s)
Imoto et al.Examiner
Deepak RaoArt Unit
1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Feb 11, 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-40 ☒ are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 3-35, and 37-40 ☒ are rejected.
- 7) ☒ Claim(s) 2 and 36 ☒ are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☒ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- *See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ | 6) <input type="checkbox"/> Other: |

Art Unit: 1624

DETAILED ACTION

This office action is in response to the amendment filed on February 11, 2003.

Claims 1-40 are pending in this application.

Election/Restriction

Applicant's election of Group II, claims 1-34 (in part) drawn to tetrahydropyrimidine compounds in Paper No. 6 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Note: Affirmation of the election was not made by the applicant which was required in the previous office action.

Applicant also elected Compound No. 2 (page 29, Table 1) as the species for examination. The species represents a compound of formula (I) wherein A^1 and R^7 - R^{12} are hydrogen and A^2 is 6-chloro-pyrid-3-yl. The elected species was not found in the prior art and the search was expanded (as per the guidelines of MPEP § 803.02) to compounds of formula (I) wherein X is $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$; A^1 is H and A^2 is optionally substituted pyridyl and art was found.

The subject matter of compounds of formula (I) wherein X is $-(\text{CR}^1, \text{R}^2)-\text{C}(\text{R}^3, \text{R}^4)-$, $-\text{C}(\text{R}^5)=\text{C}(\text{R}^6)-$, $-\text{C}(\text{R}^{13}, \text{R}^{14})-\text{C}(\text{R}^{15}, \text{R}^{16})-\text{NH}-$ and species of imidazoline, 1,2,4-triazine, etc. in claim 2 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Art Unit: 1624

The following rejections are withdrawn:

The rejections under 35 U.S.C. 112, second paragraph of the previous office action are withdrawn in view of the amendments.

The following rejections are maintained:

1. Claims 5-21 and 26-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of the diseases that require an activator for $\alpha 4\beta 2$ nicotinic acetylcholine receptors, does not reasonably provide enablement for **preventing** of the same. The reasons provided in the previous office action are incorporated here by reference.

Applicant's arguments and the Declaration by Dr. Tani are fully considered but they were not deemed to be persuasive. Based on the results provided in the declaration, Dr. Tani concludes that the compounds of the instant claims have $\alpha 4\beta 2$ agonistic activity and therefore, "**may exhibit potential** cognition-enhancing properties in animal model of Alzheimer's disease". However, there is no conclusive evidence that the compounds are useful in "preventing" all of the diseases, including Alzheimer's disease, etc.

As indicated in the previous office action, **preventing** actually means to anticipate or counter in advance or to keep from happening and applicant has not provided any guidance related to this issue, neither in the disclosure nor in the prior art. First, applicant relies on the $\alpha 4\beta 2$ agonistic activity of the compounds to support the instant claims, however, applicant has

Art Unit: 1624

not provided any evidence to the effect that the instant compounds are useful in “**preventing**” the recited conditions in general. The administration techniques provided in the specification are common practice of ‘therapeutic treatment’ which is known to the skilled artisan. The claims specifically recite ‘**preventing**’ of the diseases, which means to ‘counter in advance’ and not as a follow-up of a treatment by which the composition has already been administered.

Discussion based on several references clearly highlighting the unpredictability of the claimed activity have been provided in the previous office action. Further, MPEP § 2164.02 clearly states that a reasonable *in vitro/in vivo* correlation needs to be established for the claimed activity, which is clearly lacking in the instantly claimed ‘**preventing**’ activity. Applicants has not provided sufficient basis to conclude that the instantly claimed compounds can be used in **preventing** various diseases of the claims. In view of the above, it is maintained that the specification is enabling for the use of the claimed $\alpha 4\beta 2$ agonists in treatment of the diseases and does not provide for the **prevention** of the same.

2. Claims 1, 3-9 and 14-18 are rejected under 35 U.S.C. 102(a) as being anticipated by Maguire et al., WO 01/10842 (published Feb 15, 2001), for the reasons provided in the previous office action which are incorporated here by reference.

3. Claims 1, 3-9 and 14-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Kolaczowska et al., Chem. Abstract 112:35878, for the reasons provided in the previous office action which are incorporated here by reference.

Art Unit: 1624

4. Claims 1, 3-9 and 14-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Frei et al., GB 2082577, for the reasons provided in the previous office action which are incorporated here by reference.
5. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Kwok, Chem. Abstract 89:179949, for the reasons provided in the previous office action which are incorporated here by reference.
6. Claims 1, 3-21 and 26-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Walker et al., Chem. Abstract 87:111268, for the reasons provided in the previous office action which are incorporated here by reference.
7. Claims 1, 3-21 and 26-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Upshall, Chem. Abstract 77:70055, for the reasons provided in the previous office action which are incorporated here by reference.

Applicant's arguments for each of the rejections under 102 are fully considered but they were not deemed to be persuasive. Applicant argues that 'the reference compounds are clearly different from the claimed invention'. However, the claim recites A² to be "an optionally substituted heterocyclic group" and each of the references used in the rejections above provide an 'optionally' substituted pyridyl group attached to the 2-position of the 1,4,5,6-tetrahydropyrimidine.

Art Unit: 1624

Maguire et al. (WO'842) discloses a 1,4,5,6-tetrahydropyrimidine substituted at the 2-position by a pyrid-3-yl group having a 2-position substituent of [(2-methoxy-5-nitrophenyl)methyl]thio which fits the recitation of an 'optional substituent'.

Kolaczowska et al., discloses a 1,4,5,6-tetrahydropyrimidine substituted at the 2-position by an unsubstituted pyrid-2-yl or a 4-amino-pyrid-3-yl, both of which correspond to the instant recitation of an 'optionally substituted heterocyclic group'.

Similarly, the other references also disclose 1,4,5,6-tetrahydropyrimidine having 'an optionally substituted pyridyl group' attached to the 2-position.

Applicant has not provided how these compounds differ from the claimed invention.

The following rejections are necessitated by the amendment:

1. Claims 22-25 are rejected under 35 U.S.C. 102(a) as being anticipated by Maguire et al., WO 01/10842. Claims 22-25 are rejected under 35 U.S.C. 102(b) as being anticipated by:

(a) Kolaczowska et al., 112:35878

(b) Frei et al., GB 2082577

(c) Kwok, 89:179949

(d) Walker, 87:111268, or

(e) Upshall, 77:70055, for the reasons provided in the previous office action.

The above claims were not treated on merits in the previous office action.

Art Unit: 1624

2. Claims 1, 3-9, 35 and 37-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Munro et al., WO 94/22851. The instantly claimed compounds read on the reference disclosed compounds, see compounds of Example 1 (page 9), Examples 4 and 7 in Table 1 (page 11) and Example 9 (page 12). The instant claim 35 recites that 'A¹ and A² are each a hydrogen atom, optionally substituted alkyl group or heterocyclic group selected from pyridine substituted with one or more of halogen atom'. The reference disclosed compound, e.g., Example 4 is identical to the claimed compound of formula (I) wherein A¹ is 6-chloro-3-pyridyl; A² is dichloronitromethyl and R⁷-R¹² are hydrogen. The intended use recitation in the composition claims is not given any patentable weight.

Note: Claims 1 and 35 read on 1,4,5,6-tetrahydropyrimidine which is available in Aldrich catalog 29333-4.

Duplicate Claims

Applicant is advised that should claims 3-4 be found allowable, claims 5-9 and 14-18 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In the instant case, claims 5-9 and 14-18 recite an intended use of the composition or medicament without setting

Art Unit: 1624

forth any positive steps or limitations and accordingly, they are substantial duplicates of claims 3 and 4 respectively.

Applicant did not respond to the above warning in the amendment filed on February 11, 2003.

Allowable Subject Matter

Claim 36 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 2 is objected to as being dependent upon a rejected base claim **and** for containing non-elected subject matter, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims and limited to the elected subject matter of tetrahydropyrimidines.

Conclusion

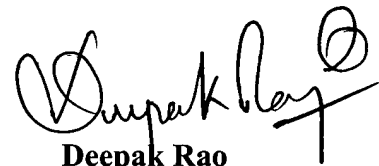
Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

Art Unit: 1624

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (703) 305-1879. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

A handwritten signature in black ink, appearing to read 'Deepak Rao', with a stylized flourish at the end.

Deepak Rao
Primary Examiner
Art Unit 1624

May 5, 2003